ORIGINAL PAPER



Risk stratification in acute coronary syndrome: Evaluation of the GRACE and CRUSADE scores in the setting of a tertiary care centre

Katharina Tscherny | Calvin Kienbacher | Verena Fuhrmann | Raphael van Tulder | Wolfgang Schreiber | Harald Herkner | Dominik Roth

Department of Emergency Medicine, Medical University of Vienna, Vienna, Austria

Correspondence

Harald Herkner, Department of Emergency Medicine, Medical University of Vienna, Waehringer Guertel 18-20/6D, Vienna A-1090, Austria.

Email: harald.herkner@meduniwien.ac.at

Abstract

Objective: Risk assessment plays a decisive role in the management of acute coronary syndrome (ACS). The GRACE and the CRUSADE scores are among the most frequently used risk assessment tools. We aimed to compare the performance of the GRACE and CRUSADE risk scores to predict in-hospital mortality and major bleeding in a contemporary ACS population at a high-volume academic hospital.

Methods: All patients treated for ACS from January 1, 2006 to December 31, 2015 at a tertiary care centre were prospectively enrolled. We calculated GRACE and CRUSADE risk scores. We compared the discrimination capacity of both scores for in-hospital mortality and major bleeding.

Results: In total 4087 patients (1151 [28.2%] female; age 62 ± 14 years) were included. Among these 2218 (54.3%) were diagnosed with ST-elevation myocardial infarction, 113 (2.8%) died in hospital and major bleeding occurred in 65 (1.6%). Discrimination capacity for in-hospital mortality of the GRACE score was superior to the CRUSADE score (receiver operator characteristic area under the curve (AUC) 0.91 (95% CI 0.89-0.93) vs 0.83 (95% CI 0.80-0.86); P < .01). Performance for major bleeding differed but was poor for both scores (AUC 0.71 [0.65-0.76] for GRACE vs 0.61 [0.55-0.68] for CRUSADE; P < .01).

Conclusion: The GRACE score appears to be superior over CRUSADE to predict inhospital mortality. Major bleeding is rare in the era of primary PCI and performance of both scores for this outcome was poor.

1 | INTRODUCTION

1.1 | Background

Coronary artery disease (CAD) is the single most frequent cause of death worldwide. More than seven million people die from CAD every year, accounting for 12.8% of all deaths. Acute coronary syndrome (ACS) is a potentially life-threatening manifestation of CAD, where time is crucial in the initial management.

A mainstay of the initial management is based on ischaemic and bleeding risk stratification, as recommended in current international clinical guidelines. 2,3

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The 'Global Registry of Acute Coronary Events' (GRACE) and the 'Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines' (CRUSADE) scores are among the most frequently used risk assessment tools. ^{2,4,5}

GRACE was developed involving more than 40 000 patients presenting with ACS as a clinical risk prediction tool for estimating the cumulative 6-month risk of death and death or myocardial infarction to facilitate triage and management of patients with ACS. GRACE is not restricted to any ST segment alterations. The CRUSADE-score was developed from a cohort of NSTEMI patients by Subherwal et al (2009) to estimate baseline risk of in-hospital major bleeding, and mortality and validated in more than 70 000 patients. The GRACE and CRUSADE score have several similarities and tend to be used exchangeable in clinical practice (Table 1).

A recent study suggested superiority of the GRACE over the CRUSADE score to predict in-hospital mortality and major bleeding in a cohort of 1587 ACS patients. Accordingly, it appears desirable to reappraise the comparison of these globally used scores.

1.2 | Importance

Cardiovascular diseases (CVD) are the number one cause of death globally. About 17.9 million people died from CVDs in 2016. It represented 31% of all global deaths, 85% of which occurred because of heart attack or stroke. These diseases lead to serious consequences such as disability or sudden death. As a result, there are high monetary costs related to the management of these diseases imposing a severe burden for the healthcare system. Limited resources demand prudent and evidence based use of means, yet only one study compared these two scores.

1.3 | Goals of this investigation

We aimed to compare GRACE and CRUSADE risk scores to predict in-hospital mortality and major bleeding in patients, presenting to a high-volume academic emergency department, who were diagnosed with ACS.

TABLE 1 GRACE and CRUSADE score parameters

GRACE score	CRUSADE score		
Creatinine level	Creatinine clearance		
Heart rate	Heart rate		
Systolic blood pressure	Systolic blood pressure		
Killip class	Signs of CHF at presentation		
Age	Sex		
Cardiac arrest at admission	Baseline haematocrit		
ST-segment deviation	Prior vascular disease		
Elevated cardiac enzyme levels	Diabetes mellitus		

Abbreviation: CHF, congestive heart failure.

What's known

- Risk management is essential for the management of acute coronary syndrome.
- The GRACE and CRUSADE scores are amongst the most widely used tools to estimate risk of death or major bleeding.

What's new

- The GRACE score has good prediction capability for in-hospital death in patients with acute coronary syndrome, and is superior to CRUSADE.
- It is also better than CRUSADE to predict major bleeding, although the latter score was specifically developed for bleeding.

2 | METHODS

2.1 | Study design & setting

This is a cohort study in patients with the diagnosis of ACS according to ESC criteria⁸ at the emergency department from January 2006 to December 2015. The setting is a 2200-beds tertiary care academic centre. The department of emergency medicine is responsible for the management of all (possibly) life-threatening emergencies, except for trauma, psychiatry and paediatrics. At the department around 80 000 patients are treated per year, including approximately 700 patients with acute myocardial infarction. The study was conducted according to the Declaration of Helsinki. It was approved by the institutional review board.

2.2 | Methods and measurements

All eligible patients were prospectively enrolled in a registry according to the Cardiology Audit and Registration Data Standards (CARDS) of the European Society of Cardiology.¹⁰

The registry contains demographics, cardiovascular risk factors, previous medical history, symptoms, vital parameters, ECG- and laboratory findings, previous and current medication, interventions, findings from coronary angiography and complications, including death. Both GRACE and CRUSADE risk scores were calculated individually from registry information.

2.3 | Outcomes

In-hospital mortality was retrieved from the hospital information system. Major bleeding was defined according to the CRUSADE definition.⁵

2.4 | Analysis

We present categorical data as count and relative frequency, and metric data as mean ± standard deviation or median with

TABLE 2 Patients characteristics

ABLE 2 Patients characteristics	
	N = 4087
Patient characteristics	
Demographics	
Age (years)—mean ± SD	62 ± 14
Female—n (%)	1151 (28.2%)
Body weight(kg)—mean ± SD	82 ± 22
Body mass index—mean ± SD	27.6 ± 5.1
Cardiovascular risk factors	
Smoking—n (%)	1337 (32.7%)
Diabetes mellitus—n (%)	807 (19.8%)
Hypertension—n (%)	2112 (51.7%)
Family history of cardiovascular disease—n (%)	486 (11.9%)
Hyperlipidaemia—n (%)	1088 (26.6%)
Cardiovascular history	
Cerebral artery disease—n (%)	264 (6.5%)
Peripheral artery disease—n (%)	225 (5.5%)
Prior myocardial infarction—n (%)	692 (16.9%)
Prior PCI—n (%)	629 (15.4%)
Prior CABG-n (%)	174 (4.3%)
Signs and symptoms	
Typical chest pain—n (%)	2699 (66.0%)
Systolic blood pressure (mm Hg)—mean ± SD	136 ± 28
Diastolic blood pressure (mm Hg)—mean ± SD	77 ± 66
Heart rate(bpm)—mean ± SD	80 ± 16
Killip class	
Killip 1-n (%)	2846 (69.6%)
Killip 2–n (%)	183 (4.5%)
Killip 3-n (%)	83 (2.0%)
Killip 4-n (%)	114 (2.8%)
Myocardial infarction	
Туре	
STEMI-n (%)	2218 (54.3%)
NSTEMI-n (%)	1869 (45.7%)
Cardiac enzymes on admission	
Troponin T(ng/l)—median (IQR)	9 (IQR 3-39)
CK(U/I)—median (IQR)	172 (IQR 102-365)
CK-MB(U/I)—median (IQR)	53 (IQR 31-101)
Treatment strategies	
PCI-n (%)	2973 (72.7%)
CABG-n (%)	137 (3.4%)
Thrombolytic therapy—n (%)	92 (2.3%)
Coronary angiography findings	
One vessel disease	2310 (77.7%)
Two vessel disease	365 (12.3%)

(Continues)

TABLE 2 (Continued)

	N = 4087
Three vessel disease	298 (10.0%)
Complications	
Major bleeding—n (%)	65 (1.6%)

Abbreviations: CABG, coronary artery bypass grafting; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain; IQR, inter quartile range; NSTEMI, Non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI-ST, segment elevation myocardial infarction.

interquartile range, as appropriate. We classified patients into three categories of GRACE risk score (low risk: <109 points, intermediate risk: 109 to 140 points, and high risk: >140 points) and CRUSADE risk score (very low/low risk: <31 points; moderate risk: 31 to 40 points; and high/very high risk: >40 points). We formally compared the classification of the two scores using an extension of the McNemar Bowker test.

We assessed discrimination for in-hospital mortality and major bleeding of both scores on the original scale for the two scores using the areas under the curve (AUC) of the receiver operating characteristic curves. We calculated 95% confidence intervals and compared the AUCs using the non-parametric method suggested by DeLong et al.¹¹

Microsoft Excel (Microsoft Corp.) and Stata 14.0 (Stata Corp.) were used for data analysis. A two-sided *P*-value of < .05 was generally considered statistically significant.

3 | RESULTS

3.1 | Characteristics of study subjects

From January 1, 2006 to December 31, 2015, we included 4087 consecutive patients with a diagnosis of ACS. Among those 1151 (28.2%) were female. Mean age was 62 ± 14 years, and 2218 (54.3%) patients were diagnosed with STEMI. Overall 2973 (72.7%) patients underwent acute PCI, and 92 (2.3%) patients received thrombolytic therapy (see Table 2 for details).

3.2 | Main results

During the hospital stay 113 (2.8%) patients died. Major bleeding events occurred in 65 (1.6%) patients. Based on GRACE risk categories 1031 patients (25.2%) were at low risk, 1401 patients (34.3%) were at intermediate risk and 1655 patients (40.5%) were at high risk. Based on CRUSADE categories 1505 patients (36.8%) were at very low/low risk, 924 patients (22.6%) were at moderate risk and 1658 patients (40.6%) were at high/very high risk (see Figure 1 for a comparison of risk distribution between scores).

Overall risk classification differed significantly between GRACE and CRUSADE score (P < .001). This difference was mainly driven by the two lower risk categories (see Figure 1).

3.2.1 | Discrimination

In-hospital mortality

For in-hospital death the AUC of the GRACE score was 0.91 (95% CI 0.89 to 0.93), and 0.83 (95% CI 0.80 to 0.86) for the CRUSADE Score, respectively. The AUCs differed significantly between the two scores (P < .01) (see Figure 2).

Major bleeding

The AUC for major bleeding was 0.71 (95% CI 0.65 to 0.76) for the GRACE score and 0.61 (95% CI 0.55 to 0.68) for the CRUSADE Score. The AUCs differed significantly between the two scores (P < .01). See Figure 3.

4 | DISCUSSION

Although both GRACE and CRUSADE score were developed for risk assessment in patients with ACS, the background of the two scores nevertheless differs. GRACE was primarily developed to predict in-hospital mortality in patients with both ST-elevation- and non-ST-elevation-ACS. CRUSADE was developed from a cohort of NSTEMI-patients, with a primary focus on bleeding. Nevertheless, both scores are currently used in broad ACS-populations to assess the risk of both mortality and bleeding.

Comparing GRACE and CRUSADE, of eight items, respectively, only two items are identical (heart rate and systolic blood pressure), and additional two items are very similar (creatinine clearance vs creatinine level, and "signs of CHF at presentation" vs Killip Class). In line with the initial development populations, in our analysis, GRACE was superior to CRUSADE to predict mortality. In addition, although CRUSADE was primarily developed to assess risk of major bleeding, GRACE performed superior to CRUSADE for this outcome, too.

Our study adds to previous similar analysis, adding real-world data from a large tertiary care centre over a 10-year period. The proportion of patients with STEMI in our study is larger (54%) than

in most other studies. This could be explained by the fact that our hospital serves as a tertiary care academic referral centre. On two of seven days a week, it provides the only cathlab service for a two million metropolitan area, and all patients with STEMI are treated there.

Elbarouni et al validated the GRACE Score in a Canadian population of 12 424 ACS patients during a 7-year period and found excellent discrimination (c = 0.84, 95% CI 0.82-0.86, P < .001) for inhospital mortality. Similar results were found by Araújo Goncalves et al in a small cohort of 460 ACS patients from Spain (AUC 0.72; 95% CI 0.67-0.76). 13

Abu-Assi et al demonstrated excellent performance (c > 0.80) of the GRACE score even in a cohort of patients with chronic renal failure and diabetes mellitus, although it was previously suggested that the GRACE score underestimated the risk with these two comorbidities. In the subgroups undergoing PCI and patients, who did not receive PCI there were seen similar results.¹⁴

The GRACE risk score validity has been tested in multiple studies with ACS patients. 12,13,15 Wang et al aimed to improve the

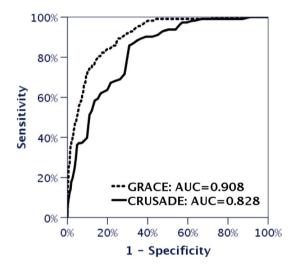


FIGURE 2 Discrimination for in-hospital mortality of the GRACE score (AUC 0.908) was superior to the CRUSADE score (AUC 0.828); P < .01. AUC, area under the curve

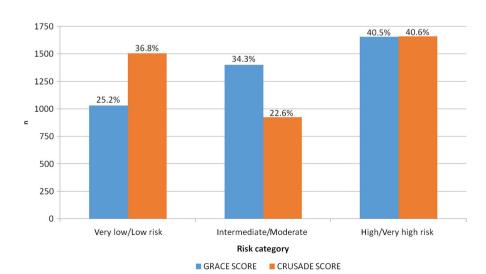


FIGURE 1 Risk category according to GRACE vs CRUSADE score

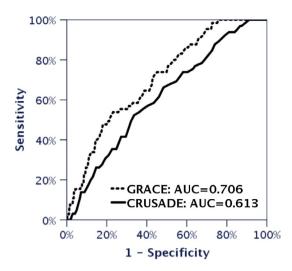


FIGURE 3 Discrimination for major bleeding was moderate for both scores (GRACE AUC 0.706 vs CRUSADE AUC 0.613; P < .01). AUC, area under the curve

GRACE Score and enrolled 13 686 Canadian ACS patients from 1999-2008. Patients were divided into three subgroups (0, 1-2 and 3-4 risk factors). They concluded that the number of risk factors does not enhance the prognostic value over the validated GRACE risk score.¹⁵

Bleeding complications are long known as an important outcome parameter in the management of ACS patients because of the fact they are associated with a worse outcome and higher costs. Therefore, various bleeding risk scores have been integrated to the daily clinical practice. Although most of them were developed from randomised clinical studies, and not by assessment of risk factors in large 'real world' cohorts. This might limit their generalisability to the general ACS population. 16,17 Current guidelines recommend the use of the CRUSADE score for bleeding risk stratification. 8,18,19

In a cohort of 4500 ACS-patients, Abu-Assi et al found the CRUSADE to have highest accuracy to predict major bleeding complications in STEMI and NSTE-ACS compared with ACTION- and Mehran-bleeding risk scores, but did not compare it to the GRACE. 18

Amador et al first suggested that both ischaemic and bleeding risk scores could be used to predict in-hospital mortality, ischaemic events and death, reporting moderate discrimination for major bleeding and death for TIMI, GRACE and CRUSADE scores (c = 0.64, 0.58 and 0.61 for major bleeding, 0.92, 0.86 and 0.63 for death).²⁰

In the most recent analysis Manzano-Fernández investigated the use of a single score (either GRACE or CRUSADE) to predict both outcomes. They found better discrimination for GRACE compared with the CRUSADE risk score for mortality (0.86 vs 0.79; P = .018) and major bleeding (0.80 vs 0.73, P = .028). These findings are supported by our results. This remains true although our study had a much longer study period (2 years vs 10 years), larger sample size, and we used a different statistical approach (logistic regression and c-statistics, vs the method by DeLong).

A possible explanation for the differences between Manzano-Fernandez's and our findings on the one hand, and the above-mentioned studies might be the decreasing overall importance of bleeding complications in the era of primary PCI, compared with when thrombolysis still played a major role. This effect is further accentuated by the trend to increased use of radial, as compared with inguinal, punctuation approaches for PCI. The in-hospital mortality rate in our study was significantly lower than in the study by Manzano-Fernández et al (2.8% vs 4.5%). The major bleeding rate differed also (2.1% vs 1.6%). Possible explanations might include that our patients in average were younger (mean age 62 ± 14 vs 67 ± 13 years), and had less comorbidites such as diabetes (20% vs 46%), hypertension (52% vs 73%) or a history of previous PCI (15% vs 30%).

All our findings have to be regarded in context of some limitations: This was a single centre study, and findings might be less generalisable to non-tertiary care centres. It also has to be kept in mind that we performed a retrospective analysis, although of prospectively collected data following strict audit and registry standards.¹⁰

In conclusion, the results of this study support previous findings on the superiority of the GRACE vs the CRUSADE score to predict in-hospital mortality in ACS patients, and adds to the growing evidence that this score might also serve the needs to predict bleeding complications. This single-score approach could ease clinical practice for all those involved in the initial management of ACS.

CONFLICT OF INTEREST

The authors state that they do not have any conflicts of interest.

AUTHORS CONTRIBUTIONS

KT developed the design of the study, participated in data collection, planned and performed data analysis, drafted the article. CK participated in the design of the study, participated in data collection and analysis, critically revised the article. VF participated in the design of the study, participated in data collection and analysis, critically revised the article. RvT participated in the design of the study, participated in data collection and analysis, critically revised the article. WS participated in the design of the study, participated data analysis, critically revised the article, supervised the whole project. HH participated in the design of the study, participated in data collection and analysis, participated in the drafting of the article. DR participated in the design of the study, participated in and supervised data analysis, participated in the drafting of the article, supervised the whole project. All authors read and approved the final version of the article.

ORCID

Dominik Roth https://orcid.org/0000-0002-3384-3675

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How to cite this article: Tscherny K, Kienbacher C, Fuhrmann V, et al. Risk stratification in acute coronary syndrome: Evaluation of the GRACE and CRUSADE scores in the setting of a tertiary care centre. *Int J Clin Pract*. 2020;74:e13444. https://doi.org/10.1111/jjcp.13444